



General

Guideline Title

Multiple sclerosis: management of multiple sclerosis in primary and secondary care.

Bibliographic Source(s)

National Clinical Guideline Centre. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 36 p. (Clinical guideline; no. 186).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Collaborating Centre for Chronic Conditions. Multiple sclerosis. National clinical guideline for diagnosis and management in primary and secondary care. London (UK): National Institute for Clinical Excellence (NICE); 2004. 197 p. [468 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

Diagnosing Multiple Sclerosis (MS)

Be aware that clinical presentations in MS include:

- Loss or reduction of vision in 1 eye with painful eye movements
- Double vision
- Ascending sensory disturbance and/or weakness
- Problems with balance, unsteadiness or clumsiness
- Altered sensation travelling down the back and sometimes into the limbs when bending the neck forwards (Lhermitte's symptom)

Be aware that usually people with MS present with neurological symptoms or signs as described above, and:

- Are often aged under 50 and
- May have a history of previous neurological symptoms and
- Have symptoms that have evolved over more than 24 hours and
- Have symptoms that may persist over several days or weeks and then improve

Do not routinely suspect MS if a person's main symptoms are fatigue, depression or dizziness unless they have a history or evidence of focal neurological symptoms or signs.

Before referring a person suspected of having MS to a neurologist, exclude alternative diagnoses by performing blood tests including:

- Full blood count
- Inflammatory markers for example erythrocyte sedimentation rate, C-reactive protein
- Liver function tests
- Renal function tests
- Calcium
- Glucose
- Thyroid function tests
- Vitamin B₁₂
- Human immunodeficiency virus (HIV) serology

Do not diagnose MS on the basis of magnetic resonance imaging (MRI) findings alone.

Refer people suspected of having MS to a consultant neurologist. Speak to the consultant neurologist if you think a person needs to be seen urgently.

Only a consultant neurologist should make the diagnosis of MS on the basis of established up-to-date criteria, such as the revised 2010 McDonald criteria¹, after:

- Assessing that episodes are consistent with an inflammatory process
- Excluding alternative diagnoses
- Establishing that lesions have developed at different times and are in different anatomical locations for a diagnosis of relapsing–remitting MS
- Establishing progressive neurological deterioration over 1 year or more for a diagnosis of primary progressive MS

If a person is suspected¹ of having MS but does not fulfil the diagnostic criteria, plan a review. Discuss the timing of the review with the person and ensure they know who to contact for advice if they develop further neurological symptoms or if current symptoms worsen.

Offer people suspected of having MS, information about support groups and national charities.

Optic Neuritis and Neuromyelitis Optica

If a person has an episode of isolated optic neuritis, confirmed by an ophthalmologist, refer them to a consultant neurologist for further assessment.

Diagnosis of neuromyelitis optica should be made by an appropriate specialist based on established up-to-date criteria.

Providing Information and Support

NICE has produced guidance on the components of good patient experience in adult National Health Service (NHS) services. This includes recommendations on communication, information and coordination of care. Follow the recommendations in the NICE guideline [Patient experience in adult NHS services](#) (NICE clinical guideline 138).

Information at the Time of Diagnosis

The consultant neurologist should ensure that people with MS and, with their agreement their family members or carers, are offered oral and written information at the time of diagnosis. This should include, but not be limited to, information about:

- What MS is
- Treatments, including disease-modifying therapies

- Symptom management
- How support groups, local services, social services and national charities are organised and how to get in touch with them
- Legal requirements such as notifying the Driver and Vehicle Licensing Agency (DVLA) and legal rights including social care, employment rights and benefits

Discuss with the person with MS and their family members or carers whether they have social care needs and if so refer them to social services for assessment. Ensure the needs of children of people with MS are addressed.

Offer the person with MS a face-to-face follow-up appointment with a healthcare professional with expertise in MS to take place within 6 weeks of diagnosis.

Ongoing Information and Support

Review information, support and social care needs regularly. Continue to offer information and support to people with MS or their family members or carers even if this has been declined previously.

Ensure people with MS and their family members or carers have a management plan that includes who to contact if their symptoms change significantly.

Explain to people with MS that the possible causes of symptom changes include:

- Another illness such as an infection
- Further relapse
- Change of disease status (for example progression)

Talk to people with MS and their family members or carers about the possibility that the condition might lead to cognitive problems.

When appropriate, explain to the person with MS (and their family members or carers if the person wishes) about advance care planning and power of attorney.

Coordination of Care

Care for people with MS using a coordinated multidisciplinary approach. Involve professionals who can best meet the needs of the person with MS and who have expertise in managing MS including:

- Consultant neurologists
- MS nurses
- Physiotherapists and occupational therapists
- Speech and language therapists, psychologists, dietitians, social care and continence specialists
- General practitioners (GPs)

Offer the person with MS an appropriate single point of contact to coordinate care and help them access services.

Modifiable Risk Factors for Relapse or Progression of MS

Exercise

Encourage people with MS to exercise. Advise them that regular exercise may have beneficial effects on their MS and does not have any harmful effects on their MS.

Vaccinations

Be aware that live vaccinations may be contraindicated in people with MS who are being treated with disease-modifying therapies.

Discuss with the person with MS:

- The possible benefits of flu vaccination and
- The possible risk of relapse after flu vaccination if they have relapsing–remitting MS

Offer flu vaccinations to people with MS in accordance with national guidelines, which recommend an individualised approach according to the person's needs.²

Pregnancy

Explain to women of childbearing age with MS that:

- Relapse rates may reduce during pregnancy and may increase 3 to 6 months after childbirth before returning to pre-pregnancy rates.
- Pregnancy does not increase the risk of progression of disease.

If a person with MS is thinking about pregnancy, give them the opportunity to talk with a healthcare professional with knowledge of MS about:

- Fertility
- The risk of the child developing MS
- Use of vitamin D before conception and during pregnancy
- Medication use in pregnancy
- Pain relief during delivery (including epidurals)
- Care of the child
- Breastfeeding

Smoking

Advise people with MS not to smoke and explain that it may increase the progression of disability (see the NICE guideline [Smoking cessation services](#) [NICE public health guideline 10]).

MS Symptom Management and Rehabilitation

The guideline does not make recommendations for all symptoms that occur in people with MS. Some symptoms are addressed in other NICE guidelines and these are referenced where appropriate.

Determine how often the person with MS will need to be seen based on:

- Their needs, and those of their family and carers and
- The frequency of visits needed for different types of treatment (such as review of disease-modifying therapies, rehabilitation and symptom management)

Fatigue

Assess and offer treatment to people with MS who have fatigue for anxiety, depression, difficulty in sleeping, and any potential medical problems such as anaemia or thyroid disease.

Explain that MS-related fatigue may be precipitated by heat, overexertion and stress or may be related to the time of day.

Offer amantadine³ to treat fatigue in people with MS.

Consider mindfulness-based training, cognitive behavioural therapy or fatigue management for treating MS-related fatigue.

Advise people that aerobic, balance and stretching exercises including yoga may be helpful in treating MS-related fatigue.

Do not use vitamin B₁₂ injections to treat fatigue in people with MS.

Consider a comprehensive programme of aerobic and moderate progressive resistance activity combined with cognitive behavioural techniques for fatigue in people with MS with moderately impaired mobility (an EDSS⁴ score of greater than or equal to 4).

Mobility

Ensure people with MS and mobility problems have access to an assessment to establish individual goals and discuss ways in which to achieve them. This would usually involve rehabilitation specialists and physiotherapists with expertise in MS.

Do not use fampridine to treat lack of mobility in people with MS because it is not a cost effective treatment.⁵

Mobility or Fatigue

Consider supervised exercise programmes involving moderate progressive resistance training and aerobic exercise to treat people with MS who have mobility problems and/or fatigue.

Mobility and/or Fatigue with Balance Problems

Consider vestibular rehabilitation for people with MS who have fatigue or mobility problems associated with limited standing balance.

Treatment Programmes for Mobility and/or Fatigue

Encourage people with MS to keep exercising after treatment programmes end for longer term benefits (see the NICE guideline [Behaviour change: individual approaches](#) [NICE public health guideline 49]).

Help the person with MS continue to exercise, for example by referring them to exercise referral schemes.

If more than one of the interventions recommended for mobility or fatigue are suitable, offer treatment based on which the person prefers and whether they can continue the activity after the treatment programme ends.

Spasticity

In people with MS assess and offer treatment for factors that may aggravate spasticity such as constipation, urinary tract or other infections, inappropriately fitted mobility aids, pressure ulcers, posture and pain.

Encourage people with MS to manage their own spasticity symptoms by explaining how doses of drugs can be adjusted within agreed limits.

Ensure that the person with MS:

- Has tried the drug at an optimal dose, or the maximum dose they can tolerate
- Stops the drug if there is no benefit at the maximum tolerated dose
- Has their drug treatment reviewed at least annually once the optimal dose has been reached

Consider baclofen or gabapentin⁶ as a first-line drug to treat spasticity in MS depending on contraindications and the person's comorbidities and preferences. If the person with MS cannot tolerate one of these drugs consider switching to the other.

Consider a combination of baclofen and gabapentin^{6,7} for people with MS if:

- Individual drugs do not provide adequate relief or
- Side effects from individual drugs prevent the dose being increased

Consider tizanidine or dantrolene as a second-line option to treat spasticity in people with MS.

Consider benzodiazepines as a third-line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms.

Do not offer Sativex to treat spasticity in people with MS because it is not a cost-effective treatment.⁸

If spasticity cannot be managed with any of the above pharmacological treatments, refer the person to specialist spasticity services.

Oscillopsia⁹

Consider gabapentin⁶ as a first-line drug to treat oscillopsia in people with MS.

Consider memantine¹⁰ as the second-line treatment for oscillopsia in people with MS.

Refer the person with MS for specialist advice if there is no improvement of oscillopsia after treatment with gabapentin and memantine or side effects prevent continued use.

Emotional Lability¹¹

Consider amitriptyline¹² to treat emotional lability in people with MS.

Pain

Treat neuropathic pain in people with MS according to the NGC summary of the NICE guideline [Neuropathic pain – pharmacological management. The pharmacological management of neuropathic pain in adults in non-specialist settings](#) (NICE clinical guideline 173) and refer to pain services if appropriate.

Be aware that musculoskeletal pain is common in people with MS and is usually secondary to problems with mobility and posture. Assess musculoskeletal pain, offer treatment to the person and refer them as appropriate.

Cognition Including Memory

Be aware that the symptoms of MS can include cognitive problems, including memory problems that the person may not immediately recognise or associate with their MS.

Be aware that anxiety, depression, difficulty in sleeping and fatigue can impact on cognitive problems. If a person with MS experiences these symptoms and has problems with memory and cognition, offer them an assessment and treatment.

Consider referring people with MS and persisting memory or cognitive problems to both an occupational therapist and a neuropsychologist to assess and manage these symptoms.

Comprehensive Review

Ensure all people with MS have a comprehensive review of all aspects of their care at least once a year.

Ensure the comprehensive review is carried out by healthcare professionals with expertise in MS and its complications. Involve different healthcare professionals with expertise in specific areas of the review if needed.

Tailor the comprehensive review to the needs of the person with MS assessing:

- MS symptoms:
 - Mobility and balance including falls
 - Need for mobility aids including wheelchair assessment
 - Use of arms and hands
 - Muscle spasms and stiffness
 - Tremor
 - Bladder (see the NGC summary of the NICE guideline [Urinary incontinence in neurological disease. Management of lower urinary tract dysfunction in neurological disease](#). [NICE clinical guideline 148]), bowel (see the NICE guideline [Faecal incontinence](#) [NICE clinical guideline 49]) and sexual function
 - Sensory symptoms and pain
 - Speech and swallowing (see the NICE guideline [Nutrition support in adults](#) [NICE clinical guideline 32])
 - Vision
 - Cognitive symptoms
 - Fatigue
 - Depression (see the NICE guideline [Depression in adults with a chronic physical health problem. Treatment and Management](#) [NICE clinical guideline 91]) and anxiety (see the NGC summary of the NICE guideline [Generalised anxiety disorder and panic disorder \[with or without agoraphobia\] in adults. Management in primary, secondary and community care](#) [NICE clinical guideline 113])
 - Sleep
 - Respiratory function
- MS disease course:
 - Relapses in last year
- General health:
 - Weight
 - Smoking, alcohol and recreational drugs
 - Exercise
 - Access to routine health screening and contraception
 - Care of other chronic conditions
- Social activity and participation:
 - Family and social circumstances
 - Driving and access to transport
 - Employment
 - Access to daily activities and leisure
- Care and carers:

- Personal care needs
- Social care needs
- Access to adaptations and equipment at home

Refer any issues identified during the comprehensive review of the person with MS to members of the MS multidisciplinary team and other appropriate teams so that they can be managed.

Ensure people with MS are offered a medication review in line with the NICE guideline [Medicines adherence. Involving patients in decisions about prescribed medicines and supporting adherence](#) [] (NICE clinical guideline 76).

Ensure people with MS have their bone health regularly assessed and reviewed in line with the NGC summary of the NICE guideline [Osteoporosis: assessing the risk of fragility fracture](#) (NICE clinical guideline 146).

Ensure people with MS and severely reduced mobility are regularly assessed and reviewed for risk of contractures¹³.

Check people with MS and severely reduced mobility at every contact for areas at risk of pressure ulcers (see the NGC summary of the NICE guideline [Pressure ulcers: prevention and management of pressure ulcers](#) [NICE clinical guideline 179]).

Discuss the care provided by carers and care workers as part of the person's care plan. Ensure carers know about their right to a local authority carer's assessment and how to apply for one.

Refer people with MS to palliative care services for symptom control and for end of life care when appropriate.

Relapse and Exacerbation

Treating Acute Relapse of MS with Steroids

Develop local guidance and pathways for timely treatment of relapses of MS. Ensure follow-up is included in the guidance and pathway.

Non-specialists should discuss a person's diagnosis of relapse and whether to offer steroids with a healthcare professional with expertise in MS because not all relapses need treating with steroids.

Recognising a Relapse

Diagnose a relapse of MS if the person:

- Develops new symptoms or
- Has worsening of existing symptoms

And these last for more than 24 hours in the absence of infection or any other cause after a stable period of at least 1 month.

Before diagnosing a relapse of MS:

- Rule out infection – particularly urinary tract and respiratory infections and
- Discriminate between the relapse and fluctuations in disease or progression

Assess and offer treatment for relapses of MS, that affect the person's ability to perform their usual tasks, as early as possible and within 14 days of onset of symptoms.

Do not routinely diagnose a relapse of MS if symptoms are present for more than 3 months.

Treating a Relapse

Offer treatment for relapse of MS with oral methylprednisolone 0.5 g daily for 5 days.

Consider intravenous methylprednisolone 1 g daily for 3 to 5 days as an alternative for people with MS:

- In whom oral steroids have failed or not been tolerated or
- Who need admitting to hospital for a severe relapse or monitoring of medical or psychological conditions such as diabetes or depression

Do not prescribe steroids at lower doses than methylprednisolone 0.5 g daily for 5 days to treat an acute relapse of MS.

Do not give people with MS a supply of steroids to self-administer at home for future relapses.

Information About Treating a Relapse with Steroids

Discuss the benefits and risks of steroids with the person with MS, taking into account the effect of the relapse on the person's ability to perform their usual tasks and their wellbeing.

Explain the potential complications of high-dose steroids, for example temporary effects on mental health (such as depression, confusion and agitation) and worsening of blood glucose control in people with diabetes.

Give the person with MS and their family members or carers (as appropriate) information that they can take away about side effects of high-dose steroids in a format that is appropriate for them.

Ensure that the MS multidisciplinary team is told that the person is having a relapse, because relapse frequency may influence which disease-modifying therapies are chosen and whether they need to be changed.

Medical, Therapy and Social Care Needs at Time of Relapse or Exacerbation

Identify whether the person having a relapse of MS or their family members or carers have social care needs and if so refer them to social services for assessment.

Offer inpatient treatment to the person having a relapse of MS if their relapse is severe or if it is difficult to meet their medical and social care needs at home.

Explain that a relapse of MS may have short-term effects on cognitive function.

Identify whether the person with MS having a relapse or exacerbation needs additional symptom management or rehabilitation.

Other Treatments

Vitamin D

Do not offer vitamin D solely for the purpose of treating MS.

Omega Fatty Acids Compounds

Do not offer omega-3 or omega-6 fatty acid compounds to treat MS. Explain that there is no evidence that they affect relapse frequency or progression of MS.

Footnotes

¹Polman CH, Reingold SC, Banwell B et al. (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology* 69:292–302.

²Chronic neurological disease: conditions in which respiratory function may be compromised, due to neurological disease (e.g., polio syndrome sufferers). Clinicians should consider on an individual basis the clinical needs of patients including individuals with cerebral palsy, multiple sclerosis and related or other similar conditions; or hereditary and degenerative disease of the nervous system of muscles; or severe disability.' (Department of Health 2013)

³At the time of publication (October 2014), amantadine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the [General Medical Council's Good practice in prescribing medicines – guidance for doctors](#) for further information.

⁴Expanded Disability Status Scale.

⁵This recommendation does not apply to people who have already started treatment with fampridine in the NHS who should be able to continue treatment until they and their NHS clinician think it appropriate to stop.

⁶At the time of publication (October 2014), gabapentin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the [General Medical Council's Good practice in prescribing medicines – guidance for doctors](#) for further information.

⁷Use caution when using gabapentin and baclofen in combination. For more information on cautions for these drugs see the summary of product

characteristics for gabapentin and baclofen and the British National Formulary.

⁸This recommendation does not apply to people who have already started treatment with Sativex in the NHS who should be able to continue treatment until they and their NHS clinician think it appropriate to stop.

⁹The subjective sensation of horizontal and/or vertical movement of the visual field that is unexplained by movement of the observer or environment.

¹⁰At the time of publication (October 2014), memantine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the [General Medical Council's Good practice in prescribing medicines – guidance for doctors](#) for further information.

¹¹Involuntary laughing and crying related to a frontal lobe lesion.

¹²At the time of publication (October 2014), amitriptyline did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the [General Medical Council's Good practice in prescribing medicines – guidance for doctors](#) for further information.

¹³A contracture is a shortening in the soft tissues (that is, tendons, muscles or ligaments) around a joint that limits the passive (and active) range of movement at that joint.

Definitions:

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer...') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Clinical Algorithm(s)

A NICE care pathway titled "Multiple Sclerosis Overview" is available from the [National Institute for Health and Care Excellence \(NICE\) Web site](#) .

Scope

Disease/Condition(s)

Multiple sclerosis (MS)

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Nursing

Nutrition

Physical Medicine and Rehabilitation

Psychiatry

Psychology

Speech-Language Pathology

Intended Users

Advanced Practice Nurses

Dietitians

Health Care Providers

Hospitals

Nurses

Occupational Therapists

Physical Therapists

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Public Health Departments

Social Workers

Speech-Language Pathologists

Guideline Objective(s)

- To cover diagnosis, information and support, treatment of relapse and management of multiple sclerosis (MS)-related symptoms

- To offer best practice advice on the care of adults with MS

Target Population

Adults who have a diagnosis of multiple sclerosis (MS) or possible MS or are being investigated for MS

Note: The guideline does not include children and young people under the age of 18 years who have a diagnosis of MS or possible MS, or are being investigated for MS.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Evaluation of neurological and other symptoms
2. Laboratory tests including full blood count, erythrocyte sedimentation rate, C-reactive protein, liver and renal function tests, calcium, glucose, thyroid function tests, vitamin B₁₂, human immunodeficiency virus (HIV) serology
3. Referral to consultant neurologist
4. Use of revised 2010 McDonald diagnostic criteria for multiple sclerosis (MS)
5. Assessment for optic neuritis and neuromyelitis optica

Management/Treatment

1. Providing patients and carers with information and support
2. Providing coordinated multidisciplinary care
3. Encouraging exercise
4. Discussing risks and benefits of flu vaccination and live vaccinations
5. Discussing pregnancy in women of childbearing age with MS
6. Advising people not to smoke
7. Managing MS symptoms
 - Amantadine for fatigue
 - Mindfulness-based training
 - Cognitive behavioural therapy
 - Aerobic and moderate progressive resistance activity
 - Vestibular rehabilitation for balance problems
 - Baclofen and gabapentin as first-line drugs for spasticity
 - Tizanidine or dantrolene as second-line drugs for spasticity
 - Benzodiazepines as third-line drugs for spasticity
 - Gabapentin (first-line) or memantine (second-line) for oscillopsia
 - Amitriptyline for emotional lability
 - Treatment of neuropathic and musculoskeletal pain
 - Referral for cognitive problems
8. Comprehensive review of care at least once per year
9. Treating acute relapse of MS with steroids (oral or intravenous methylprednisolone)
10. Recognizing/diagnosing relapse symptoms
11. Discussing risks and benefits of steroids with patients and families
12. Identifying other medical, therapy, and social care needs at times of relapse or exacerbation
13. Other treatments (vitamin D and omega fatty acid compounds not recommended for MS treatment)

Note: The following were considered but not recommended: vitamin B₁₂ injections for fatigue, fampridine for mobility problems, Sativex for spasticity.

Major Outcomes Considered

- Health-related quality of life (e.g., EuroQOL five dimensions questionnaire [EQ-5D], SF-36, Leeds MS quality of life scale, MS Impact

Scale)

- Patient-reported outcomes (e.g., symptoms, activities)
- Impact on carers
- Functional scales that quantify level of disability, such as the Expanded Disability Status Scale (EDSS), the Multiple Sclerosis Functional Composite (MSFC), the Cambridge Multiple Sclerosis Basic Score (CAMBS), the Functional Assessment of Multiple Sclerosis (FAMS) or the National Fatigue Index (NFI)
- Mobility (e.g., MS walking scale)
- Cognitive functions, such as memory and concentration
- Physical symptoms including fatigue, spasticity, spasms, assessed by validated and disease-specific scales, questionnaires or similar instruments (e.g., the Scripps Neurologic Rating scale [SNRS] or the Krupp Fatigue Severity Scale [KFSS])
- Psychological symptoms assessed by validated and disease-specific scales, questionnaire or similar instruments
- Adverse effects of treatment
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Developing the Review Questions and Outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, with a framework of population, prognostic factor and outcomes for prognostic reviews, and with a framework of key themes and population for qualitative reviews. This was to guide the literature searching process, critical appraisal and synthesis of evidence, and to facilitate the development of recommendations by the Guideline Development Group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (see Appendix A in the full version of the guideline [see the "Availability of Companion Documents" field]).

A total of 18 review questions were identified. See Table 1 in the full version of the guideline.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Searching for Evidence

Clinical Literature Search

The aim of the literature search was to systematically identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE Guidelines Manual, 2012 (see the "Availability of Companion Documents" field). Databases were searched using medical subject headings and free-text terms. Foreign language studies were not reviewed and, where possible, searches were restricted to articles published in the English language. All searches were conducted in MEDLINE, EMBASE, and the Cochrane Library, and were updated for the final time on 3rd February 2014. No papers after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F in the full version of the guideline.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were then assessed against the inclusion criteria.

Health Economic Literature Search

Systematic searches were undertaken to identify relevant health economic evidence within the published literature. The National Health Service Economic Evaluation Database (NHS EED), the Health Economic Evaluations Database (HEED) and Health Technology Assessment (HTA) database were searched using broad population terms and no date restrictions. Additionally, the search was run on MEDLINE and EMBASE using a specific economic filter, from 2009, to ensure recent publications that had not yet been indexed by the economic databases were identified. Where possible, searches were restricted to articles published in the English language. Economics search strategies are included in Appendix F in the full version of the guideline. All searches were updated for the final time on 14th February 2014. No papers published after this date were considered.

Evidence of Effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1 in the full version of the guideline:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C in the full version of the guideline). A 20% sample of the abstract lists was searched by a second reviewer to check for any potential papers that were missed. In the event of a potential missing paper being detected the entire abstract list was checked by the second reviewer.

Inclusion and Exclusion Criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C in the full version of the guideline. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix J in the full version of the guideline. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- Adults who have a diagnosis of MS or possible MS, or are having investigations for MS

The key population exclusion criterion was:

- Children and young people under the age of 18 years who have a diagnosis of MS or possible MS, or are being investigated for MS

Randomised trials, non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question, in which case the authors of the selected abstracts were contacted for further information.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

The review protocols are presented in Appendix C of the full version of the guideline.

Type of Studies

For most intervention reviews in this guideline, randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C in the full version of the guideline for full details on the study design of studies selected for each review question. For example, in the review addressing the issue of continuity of care, observational data were included because of the lack of any RCTs in the area.

For prognostic reviews, prospective and retrospective cohort studies were included. Case-control studies were not included.

Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each

study and meta-analysis was not conducted.

Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought.

The health economist:

- Undertook a systematic review of the published economic literature
- Undertook new cost-effectiveness analysis in priority areas

If both meta-analysed and narratively reported outcomes were reported, evidence statements were produced only for the meta-analysed data.

Literature Review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.

Inclusion and Exclusion Criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix F in the NICE Guidelines Manual, 2012 and the health economics review protocol in Appendix C in the full version of the guideline).

Number of Source Documents

The number of studies identified for each aspect of clinical and health economics literature is provided in Appendices D and E in the full version of the guideline, respectively (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

| Level | Description |
|-------|-------------|
|-------|-------------|

| | |
|------------|--|
| High Level | Further research is very unlikely to change confidence in the estimate of effect |
| Moderate | Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate |
| Low | Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate |
| Very Low | Any estimate of effect is very uncertain |

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Evidence of Effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1 in the full version of the guideline:

- Relevant studies were critically appraised according to the criteria specified in the checklist in "The Guidelines Manual" (see the "Availability of Companion Documents" field).
- Key information was extracted on the study's methods, patient, intervention, comparison and outcome (PICO) factors and results. These were presented in summary tables (in each review chapter) and evidence tables (see Appendix G in the full version of the guideline [see the "Availability of Companion Documents" field]).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in Guideline Development Group (GDG) meetings:
 - Randomised studies: data were meta-analysed where appropriate and reported in Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles (for intervention reviews).
 - Observational studies: data were presented as a range of values in GRADE profiles.
 - Prognostic studies: data were presented as a range of values, usually in terms of the relative effect as reported by the authors.
 - Qualitative studies: each study was summarised in a table where possible, otherwise presented in a narrative.

Methods of Combining Clinical Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software.

Sometimes where a population or treatment factor (such as gender or dose) is thought to have a strong effect on the outcome of treatments, meta-analyses will be stratified from the outset for that factor. (Note that this should be differentiated from 'sub-grouping', where post-hoc meta-analyses are done separately for different strata of pre-specified factors in an attempt to reduce serious heterogeneity existing in the overall meta-analysis. This issue is dealt within the 'Heterogeneity' section below.) However, in this guideline, the GDG did not feel that any factor would have sufficient effect on outcome to justify prior stratification of meta-analyses.

Binary Outcomes

Fixed-effects (Mantel-Haenszel) meta-analysis techniques (using an inverse variance method for pooling) were initially used to pool risk ratios (relative risk) from different studies for the binary outcomes, which included the existence/non-existence of:

- Patient-assessed symptoms
- Relapse
- Patient satisfaction
- Positive response to treatment
- Subjective improvement
- Adverse events

Absolute event rates were also calculated for binary outcomes with the GRADEpro software, using median event rate in the control arm of the pooled results.

For binary variables where there were zero events in either arm; Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events.

Where there was sufficient information provided, hazard ratios (HRs) were calculated and/or reported for outcomes such as:

- Relapse

Continuous Outcomes

The continuous outcomes were meta-analysed using an inverse variance method for pooling weighted mean differences from different studies. These outcomes included:

- Health related quality of life (HRQL)
- Patient assessed symptoms on a VAS or other subjective scale
- Level of impact on carers
- Objective measures of mobility/function/ataxia/tremor/spasticity/fatigue/pain/nystagmus
- Measures of cognitive function
- Psychological measures
- Relapse duration

Where the studies within a single meta-analysis had different scales of measurement, standardised mean differences were used, where each different measure in each study was 'normalised' to the standard deviation value pooled between the intervention and comparator groups in that same study.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals (CI) were reported, and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5.1) software. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as ' $p \leq 0.001$ ', the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in Section 16.1.3 of the Cochrane Handbook (version 5.1.0, updated March 2011). 'Missing standard deviations' were applied as the last resort, but normally the available data would be presented in the review as 'narrative results'.

Heterogeneity

Statistical heterogeneity was assessed for the overall meta-analysis estimate by considering the chi-squared test for significance at $p < 0.1$, or an I-squared inconsistency statistic of $> 50\%$, as indicating significant heterogeneity. Where significant heterogeneity was present, we normally carried out predefined sub-grouping of studies within the meta-analysis for:

1. Type of multiple sclerosis (MS): Relapsing remitting MS / Secondary progressive MS / Primary progressive MS
2. Disability: Expanded Disability Status Scale (EDSS) < 6 / EDSS > 6

These two strategies were applied in turn. If the 'type of MS' strategy managed to reduce heterogeneity to acceptable levels ($I^2 < 50\%$) within all of the derived sub-groups, then the 'disability' strategy was not used. The latter strategy was only used if the former strategy failed to resolve heterogeneity. If either of the strategies managed to reduce I^2 to less than 50% within all the derived sub-groups, then each of the derived sub-groups were adopted as separate outcomes, pending GDG 30 approval (for example, instead of the single outcome of 'existence of relapse', we would now have 'existence of relapse in people with RR MS', 'existence of relapse in people with SP MS' and 'existence of relapse in people with PP MS'. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Such subgroup differences were interpreted with caution since they broke randomisation and were subject to uncontrolled confounding.

For some questions different sub-grouping strategies were used, and this is documented in the individual question protocols.

If all pre-defined strategies of sub-grouping were unable to resolve unacceptable statistical heterogeneity within each derived sub-group, then a random effects (DerSimonian and Laird) model was employed to the entire group of studies in the meta-analysis, and sub-grouping was abandoned. A random-effects model assumes a distribution of populations, rather than a single population. This leads to a widening of the confidence intervals around the overall estimate, thus providing a more realistic interpretation of the true distribution of effects across >1 population. If, however, the GDG felt that the degree of heterogeneity was so large that meta-analysis was inappropriate, then the meta-analysis was abandoned and results were described narratively.

Special Methods

Network meta-analysis was considered for the comparison of the pharmacological treatments for spasticity, but was not used because of insufficient data available for the outcomes deemed to be most relevant to clinical decision-making.

Where studies had used a cross-over design, paired continuous data were extracted where possible, and forest plots were generated in Review manager with the Generic Inverse Variance function. For cross-over study categorical data, the standard error (of the log RR) was calculated using the simplified Mantel Haenszel method for paired outcomes, when the number of subjects with an event in both interventions was known. Again, forest plots were generated in Review manager with the Generic Inverse Variance function. If paired continuous or categorical data were not available from the cross-over studies, the separate group data were analysed in the same way as data from parallel groups, on the basis that whilst this approach would tend to over-estimate CIs and thus artificially reduce study weighting, this would be a conservative effect. Where a meta-analysis contained a mixture of studies using both paired and parallel group approaches, all data were entered into Review Manager using the Generic Inverse Variance function.

Data Synthesis for Prognostic Factor Reviews

Odds ratios (ORs), risk ratios (RRs) or HRs, with their 95% confidence intervals (95% CIs) for the effect of the pre-specified prognostic factors were extracted from the papers. Only RCTs, pooled analysis of patient level data or prospective cohort studies were included. Retrospective cohort studies were excluded because of the likelihood that data on key confounders would not have been collected, and case-control studies were excluded because of their high risk of recall bias. Prospective cohort studies were required to have a multivariable analyses, including key confounders as identified by the GDG at the protocol stage for that outcome. Data were not combined in meta-analyses for prognostic studies.

Data Synthesis for Diagnostic Test Accuracy Reviews

No diagnostic reviews were undertaken. The only review question related to diagnosis, 'what are the key diagnostic criteria for the following: multiple sclerosis, possible multiple sclerosis, neuromyelitis optica and clinically isolated syndrome?' was approached by GDG consensus rather than a formal review.

Data Synthesis for Qualitative Reviews

Findings were synthesised narratively, often organised according to the themes discussed in the literature.

Appraising the Quality of Evidence by Outcomes

Interventional Studies

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (<http://www.gradeworkinggroup.org/>). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2 in the full version of the guideline.

Details of how the four main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome and are available in the full version of the guideline. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

Prognostic Studies

The quality of evidence for prognostic studies was evaluated according to the criteria given in Table 5 in the full version of the guideline.

Because prognostic reviews were not usually based on multiple outcomes per study, quality rating was assigned by study. However if there was more than one outcome involved in a study, then the quality rating of the evidence statements for each outcome was adjusted accordingly. For

example, if one outcome was based on an invalidated measurement method, but another outcome in the same study wasn't, the latter outcome would be graded one grade higher than the other.

Quality rating started at HIGH for prospective studies, and each major limitation (see Table 5 in the full version of the guideline) brought the rating down by one increment to a minimum grade of LOW, as explained for interventional studies. For prognostic studies prospective cohort studies with a multivariate analysis are regarded as the gold standard because RCTs are usually inappropriate for these types of review.

Qualitative Reviews

Qualitative data provides information of people's thoughts, feelings, attitudes and beliefs. As such data is necessarily subjective, there is no requirement for it to be representative of the wider population; instead it is framed in the unique context of the individual respondent. Nevertheless, these data need to be trustworthy in terms of accurately reflecting the actual opinions of the respondent.

Quality was assessed using a modified version of the NICE qualitative studies appraisal framework, which can be found at Appendix I in "The Guidelines Manual" (see the "Availability of Companion Document" field).

Issues covered by this quality assessment were:

- Rigour of the research methodology
- Quality of data collection
- Clear description of role of researcher
- Clear description of context
- Trustworthy data collection methods
- Rigorous analysis methods
- Richness of data
- Trustworthy data analysis methods
- Convincing findings
- Relevance to the aims of the study

This quality assessment was carried out independently by two systematic reviewers who discussed findings to reach consensus.

Overall Grading of the Quality of Clinical Evidence

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores from each of the main quality elements (0, -1 or -2) were summed to give a score that could be anything from 0 (the best possible) to -8 (the worst possible). However scores were capped at -3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if the overall score was -1, -2 or -3 points respectively. The significance of these overall ratings is explained in Table 3 in the full version of the guideline. The reasons or criteria used for downgrading were specified in the footnotes of the GRADE tables.

On the other hand, observational interventional studies started at LOW, and so a score of -1 would be enough to take the grade to the lowest level of VERY LOW. Observational studies could, however, be upgraded if there was: a large magnitude of effect, a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect.

The details of the criteria used for each of the main quality elements are discussed further in the full version of the guideline.

Assessing Clinical Importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardised across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved (if positive) the outcome of interest in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative. For adverse events 50 participants or more per 1000 was considered to be a clinical harm.

For continuous outcomes clinical benefit, harm or no harm was based on whether the mean difference was greater than the minimally important

difference.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

Clinical Evidence Statements

Clinical evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty/uncertainty in the estimate of effect. The evidence statements were presented by outcome and encompassed the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other or whether there is no difference between the two tested treatments)
- A description of the overall quality of evidence (GRADE overall quality)

Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought.

The health economist:

- Undertook a systematic review of the published economic literature
- Undertook new cost-effectiveness analysis in priority areas

If both meta-analysed and narratively reported outcomes were reported, evidence statements were produced only for the meta-analysed data.

Literature Review

The health economist:

- Critically appraised relevant studies using the economic evaluations checklist as specified in "The Guidelines Manual" (see the "Availability of Companion Documents" field).
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix H in the full version of the guideline).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question).

NICE Economic Evidence Profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from "The Guidelines Manual" (see the "Availability of Companion Documents" field). It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 6 in the full version of the guideline for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.

Where economic studies compare multiple strategies, results are presented in the economic evidence profiles for the pair-wise comparison specified in the review question, irrespective of whether or not that comparison was 'appropriate' within the analysis being reviewed. A comparison is 'appropriate' where an intervention is compared with the next most expensive non-dominated option – a clinical strategy is said to 'dominate' the alternatives when it is both more effective and less costly. Footnotes indicate if a comparison was 'inappropriate' in the analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researches as well as lay members developed this guideline. The GDG was convened by the NCGC and chaired by Dr Paul Cooper in accordance with guidance from NICE.

The group met every 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

Developing Recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices G and H in the full version of the guideline (see the "Availability of Companion Documents" field).
- Summary of clinical and economic evidence and quality (as presented in Chapters 5–13 in the full version of the guideline).
- Forest plots and summary receiver operated characteristic (ROC) curves (see Appendix I in the full version of the guideline).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (see Chapter 11.2 in the full version of the guideline).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were done through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The main considerations specific to each recommendation are outlined in the Evidence to Recommendation Section preceding the recommendation section in the full version of the guideline.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer...') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Cost Analysis

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the Guideline Development Group (GDG) after formation of the review questions and consideration of the available health economic evidence.

The GDG identified pharmacological management of mobility with fampridine as the highest priority area for original economic modelling. Fampridine is not widely used as it is a relatively new therapy. There are currently no drug alternatives to fampridine therefore the potential impact on resources would be huge if there is an increased uptake. The clinical review identified studies comparing fampridine and placebo but no published cost effectiveness were identified. Therefore an original cost utility analysis comparing fampridine to placebo was conducted.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the National Institute for Health and Care Excellence (NICE) reference case.
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the National Clinical Guideline Centre (NCGC).

Full methods for the cost-effectiveness analysis for the pharmacological management of mobility with fampridine are described in Chapter 11 in the full version of the guideline (see the "Availability of Companion Documents" field).

Cost-effectiveness Criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in Social value judgements: principles for the development of NICE guidance'.

In the Absence of Economic Evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK National Health Service (NHS) unit costs, alongside the results of the clinical review of effectiveness evidence. Where feasible and deemed useful to inform consideration of cost-

effectiveness, outcomes reported in the clinical review were mapped to EuroQOL five dimensions questionnaire (EQ-5D) using published algorithms allowing for QALYs to be estimated.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) website when the pre-publication check of the full guideline occurs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of multiple sclerosis (MS) in primary and secondary care

See the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for additional details about benefits of specific interventions.

Potential Harms

- Even short courses of steroids are associated with adverse effects and these need to be balanced against the potential benefits. Oral steroids may present a significant risk of gastrointestinal symptoms. Other potential complications of high-dose steroids include temporary effects on mental health (such as depression, confusion and agitation) and worsening of blood glucose control in people with diabetes.
- Patients receiving baclofen are more likely to report muscle weakness, while the most commonly reported adverse event with tizanidine is drowsiness/somnolence.
- Most treatments for spasticity have adverse effects, especially tizanidine, dantrolene and gabapentin. Although successful treatment of spasticity often results in muscle weakness, this is often clinically justified by the benefits.
- Drug treatments used for oscillopsia can have significant adverse effects. Studies suggested that gabapentin causes drowsiness, nausea, fatigue and dizziness. Memantine has been reported to cause reversible neurological deterioration in multiple sclerosis (MS). Expert opinion was that gabapentin may impair balance and botulinum toxin injections can increase disability, by requiring occlusion of one eye to overcome double vision and by impairing vestibulo-ocular reflexes.
- There is a possible risk of relapse after flu vaccination in patients with relapsing-remitting MS.

For additional information regarding adverse events of treatment, refer to "Pharmacological treatment and management of mobility" in the full version of the guideline. Also see the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for additional details about harms of specific interventions.

Contraindications

Contraindications

Live vaccinations may be contraindicated in people with multiple sclerosis (MS) who are being treated with disease-modifying therapies.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summaries of product characteristics of any drugs.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. Healthcare professionals should follow the [Department of Health's advice on consent](#) . If someone does not have capacity to make decisions, healthcare professionals should follow the [code of practice that accompanies the Mental Capacity Act](#) and the supplementary [code of practice on deprivation of liberty safeguards](#) .
- NICE has produced guidance on the components of good patient experience in adult National Health Service (NHS) services. All healthcare professionals should follow the recommendations in [Patient experience in adult NHS services](#) .
- The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.
- This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the [General Medical Council's Good practice in prescribing medicines – guidance for doctors](#) for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.

Implementation of the Guideline

Description of Implementation Strategy

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

Diagnosing Multiple Sclerosis (MS)

Do not diagnose MS on the basis of magnetic resonance imaging (MRI) findings alone.

Refer people suspected of having MS to a consultant neurologist. Speak to the consultant neurologist if you think a person needs to be seen urgently.

Only a consultant neurologist should make the diagnosis of MS on the basis of established up-to-date criteria, such as the revised 2010 McDonald criteria, after:

- Assessing that episodes are consistent with an inflammatory process
- Excluding alternative diagnoses
- Establishing that lesions have developed at different times and are in different anatomical locations for a diagnosis of relapsing–remitting MS
- Establishing progressive neurological deterioration over 1 year or more for a diagnosis of primary progressive MS

Information and Support

The consultant neurologist should ensure that people with MS and, with their agreement their family members or carers, are offered oral and written information at the time of diagnosis. This should include, but not be limited to, information about:

- What MS is
- Treatments, including disease-modifying therapies
- Symptom management
- How support groups, local services, social services and national charities are organised and how to get in touch with them
- Legal requirements such as notifying the Driver and Vehicle Licensing Agency (DVLA) and legal rights including social care, employment rights and benefits

Offer the person with MS a face-to-face follow-up appointment with a healthcare professional with expertise in MS to take place within 6 weeks of diagnosis.

Coordination of Care

Care for people with MS using a coordinated multidisciplinary approach. Involve professionals who can best meet the needs of the person with MS and who have expertise in managing MS including:

- Consultant neurologists
- MS nurses
- Physiotherapists and occupational therapists
- Speech and language therapists, psychologists, dietitians, social care and continence specialists
- General practitioners

MS Symptom Management and Rehabilitation

Consider supervised exercise programmes involving moderate progressive resistance training and aerobic exercise to treat people with MS who have mobility problems and/or fatigue.

Treating Acute Relapse of MS with Steroids

Offer treatment for relapse of MS with oral methylprednisolone 0.5 g daily for 5 days.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Clinical Guideline Centre. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 36 p. (Clinical guideline; no. 186).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2004 (revised 2014 Oct)

Guideline Developer(s)

National Clinical Guideline Centre - National Government Agency [Non-U.S.]

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National Institute for Health and Care Excellence (NICE)

Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

Guideline Development Group Members: Noreen Barker, MS Clinical Nurse Specialist, The National Hospital for Neurology and Neurosurgery, UCLH NHS Foundation Trust, London; Pamela Bostock, Consultant Occupational Therapist, Neurology, Staffordshire and Stoke-on-Trent Partnership NHS Trust; Peter Brex, Consultant Neurologist, King's College Hospital NHS Foundation Trust, London; Jeremy Chataway, Consultant Neurologist, National Hospital for Neurology and Neurosurgery, UCLH NHS Foundation Trust, London; Paul Cooper (*Chair*), Consultant Neurologist, Greater Manchester Neuroscience Centre, Salford Royal Foundation Trust; Aleks de Gromoboy, Patient member; Wendy Hendrie, Specialist Physiotherapist in MS, MS Centre, Norwich; Ann Hodgson, Patient member; Susan Hourihan, Clinical

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Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all Guideline Development Group (GDG) members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B in the full version of the guideline (see the "Availability of Companion Documents" field).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Collaborating Centre for Chronic Conditions. Multiple sclerosis. National clinical guideline for diagnosis and management in primary and secondary care. London (UK): National Institute for Clinical Excellence (NICE); 2004. 197 p. [468 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the [National Institute for Health and Care Excellence \(NICE\) Web site](#) .

Availability of Companion Documents

The following are available:

- Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 611 p. (Clinical guideline; no. 186). Available from the [National Institute for Health and Care Excellence \(NICE\) Web site](#) .
- Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Appendices A-F. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 127 p. (Clinical guideline; no. 186). Available from the [NICE Web site](#) .
- Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Appendices H-M. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 298 p. (Clinical guideline; no. 186). Available from the [NICE Web site](#) .
- Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Appendix G. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 746 p. (Clinical guideline; no. 186). Available from the [NICE Web site](#) .
- Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. (Clinical guideline; no 186). Available from the [NICE Web site](#) .
- Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Costing statement. National Institute for Health and Care Excellence (NICE); 2014 Oct. 11 p. (Clinical guideline; no 186). Available from the [NICE Web site](#) .
- Are the latest government guidelines on drugs for MS sufferers good news or bad? Podcast. Available from the [NICE Web site](#) .
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Available from the [NICE Web site](#) .

Patient Resources

The following is available:

- Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Information for the public. National Institute for Health and Care Excellence (NICE); 2014 Oct. Available from the [National Institute for Health and Care Excellence \(NICE\) Web site](#)

. Also available for download as a Kindle or EPUB ebook from the [NICE Web site](#) .

Also available in Welsh from the [NICE Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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